ORIGINAL ARTICLE

Overall Survival with Ribociclib plus Endocrine Therapy in Breast Cancer

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ABSTRACT

BACKGROUND

An earlier analysis of this phase 3 trial showed that the addition of a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor to endocrine therapy provided a greater benefit with regard to progression-free survival than endocrine therapy alone in premenopausal or perimenopausal patients with advanced hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer. Here we report the results of a protocol-specified interim analysis of the key secondary end point of overall survival.

METHODS

We randomly assigned patients to receive either ribociclib or placebo in addition to endocrine therapy (goserelin and either a nonsteroidal aromatase inhibitor or tamoxifen). Overall survival was evaluated with the use of a stratified log-rank test and summarized with the use of Kaplan–Meier methods.

RESULTS

A total of 672 patients were included in the intention-to-treat population. There were 83 deaths among 335 patients (24.8%) in the ribociclib group and 109 deaths among 337 patients (32.3%) in the placebo group. The addition of ribociclib to endocrine therapy resulted in significantly longer overall survival than endocrine therapy alone. The estimated overall survival at 42 months was 70.2% (95% confidence interval [CI], 63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) in the placebo group (hazard ratio for death, 0.71; 95% CI, 0.54 to 0.95; P=0.00973 by log-rank test). The survival benefit seen in the subgroup of 495 patients who received an aromatase inhibitor was consistent with that in the overall intention-to-treat population (hazard ratio for death, 0.70; 95% CI, 0.50 to 0.98). The percentage of patients who received subsequent antineoplastic therapy was balanced between the groups (68.9% in the ribociclib group and 73.2% in the placebo group). The time from randomization to disease progression during receipt of second-line therapy or to death was also longer in the ribociclib group than in the placebo group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.55 to 0.87).

CONCLUSIONS

This trial showed significantly longer overall survival with a CDK4/6 inhibitor plus endocrine therapy than with endocrine therapy alone among patients with advanced hormone-receptor–positive, HER2-negative breast cancer. No new concerns regarding toxic effects emerged with longer follow-up. (Funded by Novartis; MONALEESA-7 ClinicalTrials.gov number, NCT02278120.)

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Although breast cancer is known to be more aggressive and to be associated with a poorer prognosis in younger women than in older women,[1,2] the recommended treatment for hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer in premenopausal and postmenopausal patients is generally similar,[3-5] with the exception of the addition of ovarian suppression in premenopausal women.[2,6] Ovarian suppression induces menopause in premenopausal patients; however, suppression may not be complete,[7] and breast cancer that develops in premenopausal women may have biologic differences from that which develops in postmenopausal women. Indeed, genetic analyses have revealed that there are differences in molecular alterations of key breast cancer driver genes, tumor-suppressor genes, and genes involved in signaling pathways between premenopausal and postmenopausal patients.[1,7-10] Premenopausal patients tend to be underrepresented in clinical trials of breast cancer.

Signaling through cyclin-dependent kinases 4 and 6 (CDK4/6) is known to promote continued cell-cycle progression and growth in cancer. In addition, specific CDK4/6 alterations lead to resistance to endocrine therapy in hormone-receptor–positive breast cancer.[11-14] In clinical trials, the combination of ribociclib and endocrine therapy has resulted in significantly longer progression-free survival than endocrine therapy alone in patients with hormone-receptor–positive, HER2-negative advanced breast cancer.[4,5,15-19]

Although multiple trials have shown a significant benefit with CDK4/6 inhibitors plus endocrine therapy with respect to progression-free survival, a significant improvement in overall survival has not been shown.[15,17-22] However, overall survival was numerically higher among patients who received a CDK4/6 inhibitor in addition to endocrine therapy than among patients who received endocrine therapy alone in the PALOMA-3 (Palbociclib: Ongoing Trials in the Management of Breast Cancer–3) trial.[23] It has been acknowledged that showing improvements in overall survival in trials involving patients with metastatic breast cancer may be challenging because of potential crossover between treatment groups and subsequent receipt of active treatments, as well as variability in previous treatment exposures between the groups.[23,24]

Ribociclib is a selective, orally available inhibitor of CDK4/6.[25] In the MONALEESA-7 (Mammary Oncology Assessment of LEE011's [Ribociclib's] Efficacy and Safety–7) trial, ribociclib plus endocrine therapy resulted in significantly longer progression-free survival than endocrine therapy alone. Here we report the results of a protocol-specified second interim analysis of overall survival.

METHODS

TRIAL DESIGN AND PATIENTS

The MONALEESA-7 trial is an international, randomized, double-blind, placebo-controlled, phase 3 trial comparing ribociclib with placebo, in addition to endocrine therapy, in premenopausal or perimenopausal women with hormone-receptor–positive, HER2-negative advanced breast cancer. Patients were randomly assigned, in a 1:1 ratio, to receive ribociclib (at a dose of 600 mg, administered orally once daily for 21 consecutive days, followed by 7 days off, for a complete cycle of 28 days) or matching placebo. Both groups received goserelin (at a dose of 3.6 mg, administered subcutaneously on day 1 of each 28-day cycle). Patients also received either a nonsteroidal aromatase inhibitor (letrozole at a dose of 2.5 mg or anastrozole at a dose of 1 mg) or tamoxifen (at a dose of 20 mg), administered orally once daily continuously. The choice of endocrine therapy was made on the basis of the patient's previous adjuvant or neoadjuvant therapy or investigator or patient preference. Crossover between the two groups was not permitted.

Eligible women were 18 to 59 years of age, were premenopausal or perimenopausal at the time of trial entry, and had histologically or cytologically confirmed hormone-receptor–positive, HER2-negative advanced breast cancer. Patients were required to have locoregionally recurrent or metastatic disease that was not amenable to curative therapy, an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (scores range from 0 to 5, with higher scores indicating greater disability), and measurable disease according to Response Evaluation Criteria in Solid Tumors, version 1.1,[26] or at least one predominantly lytic bone lesion. Patients who had received adjuvant or neoadjuvant endocrine therapy were permitted to enroll. Previous endocrine therapy in the context of advanced disease was not permitted, but patients could have received tamoxifen or an aromatase inhibitor within 14 days before randomization or

goserelin within 28 days before randomization for advanced breast cancer; these patients continued treatment with goserelin plus the same hormone agent. Patients who had received no more than one previous line of chemotherapy for advanced disease were also eligible. Previous treatment with a CDK4/6 inhibitor was not permitted.

Randomization was stratified according to the presence or absence of liver or lung metastases, previous chemotherapy for advanced disease (yes or no), and endocrine therapy (tamoxifen plus goserelin or an aromatase inhibitor plus goserelin). All patients as well as all investigators who administered treatment, assessed outcomes, and analyzed data were unaware of the group assignments. Detailed methods of this trial have been reported previously.[17] The protocol, along with the statistical analysis plan, is available with the full text of this article at NEJM.org.

END POINTS

The results regarding the primary end point, investigator-assessed progression-free survival, were reported previously.[17] Overall survival, the protocol-specified key secondary end point, was defined as the time from randomization to death from any cause. Subgroup analyses according to endocrine therapy were prespecified to be performed if the results of the analysis of overall survival in the intention-to-treat population were significant. A prespecified exploratory analysis was conducted to assess progression-free survival during receipt of second-line therapy, defined as the time from randomization to the first documented disease progression while the patient was receiving second-line therapy (as reported by the physician) or death from any cause, whichever occurred first. The time to subsequent chemotherapy was defined as the time from randomization to the beginning of the first chemotherapy after discontinuation of the trial regimen. Adverse events were monitored throughout the trial and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

TRIAL OVERSIGHT

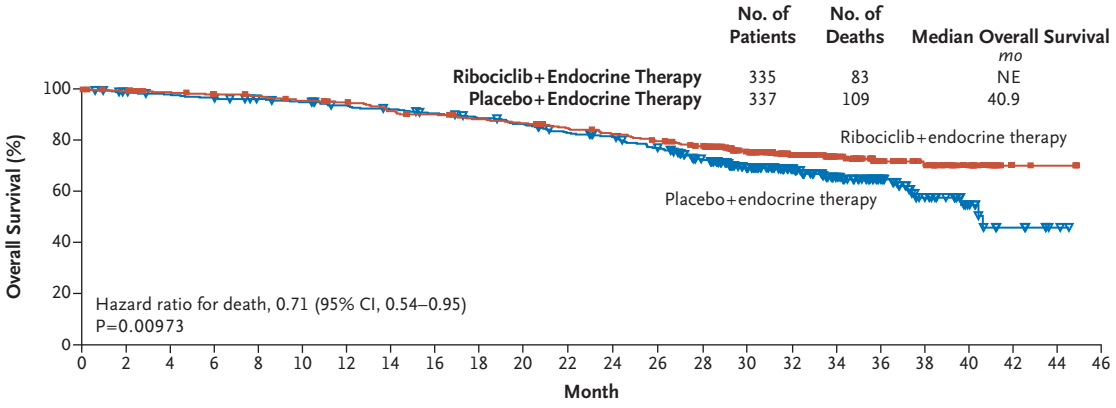
The trial was funded by Novartis and was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial protocol and all amendments were approved by an independent ethics committee or the institutional review board at each site. A trial steering committee composed of participating international investigators and representatives of the sponsor oversaw the conduct of the trial. Safety data were assessed by an independent data monitoring committee. All patients provided written informed consent before enrollment. Representatives of the sponsor designed the trial, compiled the data, and vouch for the accuracy of the analyses. All authors had access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. All authors were involved in the interpretation of the data, contributed to the writing and review of all drafts of the manuscript, and made the decision to submit the manuscript for publication. Two professional medical writers provided editorial support and were paid by the sponsor.

Table 1. Overall Survival and Kaplan–Meier Estimates.*

Variable	Ribociclib Group (N=335)	Placebo Group (N=337)
Deaths — no. (%)†	83 (24.8)	109 (32.3)
Data censored‡	252 (75.2)	228 (67.7)
Median overall survival — mo (95% CI)	NE	40.9 (37.8–NE)
Kaplan–Meier estimated overall survival (95% CI)		
24 mo	82.7 (78.1–86.5)	81.8 (77.1–85.7)
36 mo	71.9 (66.0–77.0)	64.9 (58.7–70.4)
42 mo	70.2 (63.5–76.0)	46.0 (32.0–58.9)

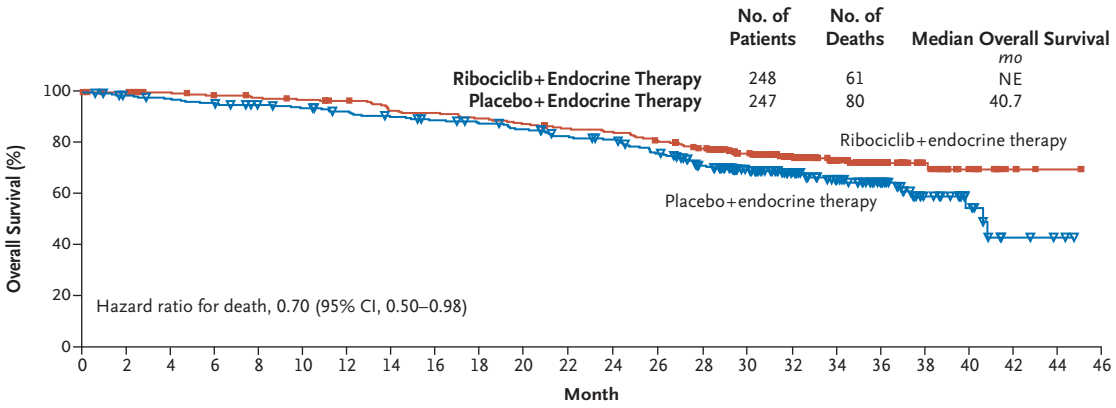
* NE indicates that the value could not be estimated.
† The hazard ratio for death was 0.71 (95% CI, 0.54 to 0.95), as calculated with the use of a stratified Cox proportional-hazards model. P=0.00973 by stratified log-rank test.
‡ Data for patients were censored at the date the patient was last known to be alive.

A All Patients



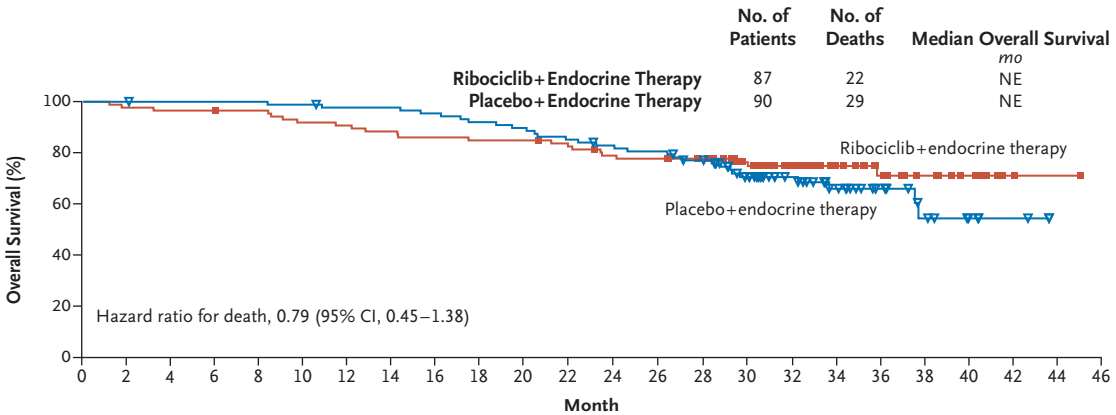
No. at Risk																							
Ribociclib	335	330	325	320	316	309	304	292	287	279	274	266	258	249	236	193	155	110	68	43	25	7	3	0
Placebo	337	330	325	321	314	309	301	295	288	280	272	258	251	235	210	166	122	92	62	33	19	7	2	0

B Patients Who Received an NSAI



No. at Risk																							
Ribociclib	248	245	241	326	233	230	226	216	213	206	201	196	192	184	174	142	113	80	49	29	16	5	2	0
Placebo	247	240	236	232	225	221	215	209	204	199	193	183	179	165	145	116	87	67	46	24	12	4	2	0

C Patients Who Received Tamoxifen



No. at Risk																							
Ribociclib	87	85	84	84	83	79	78	76	74	73	73	70	66	65	62	51	42	30	19	14	9	2	1	0
Placebo	90	90	89	89	89	88	86	86	84	81	79	75	72	70	65	50	35	25	16	9	7	3	0	0

Figure 1 (facing page). Overall Survival.
Patients with hormone-receptor–positive, human epidermal growth factor receptor 2–negative breast cancer were assigned to receive either ribociclib or placebo plus endocrine therapy with goserelin and either a nonsteroidal aromatase inhibitor (NSAI) or tamoxifen. The squares and triangles in all panels indicate censored data.
NE indicates that the value could not be estimated.

STATISTICAL ANALYSIS

The primary analysis of investigator-assessed progression-free survival was conducted at a data cutoff date of August 20, 2017, after 318 patients had had disease progression or had died. The sample size was calculated on the basis of the primary end point of progression-free survival. A hierarchical testing strategy between progression-free survival and overall survival was used to control the family-wise type 1 error rate at 2.5%.[27,28] It was determined that 252 deaths would be required for the trial to have 80% power to reject the null hypothesis of no difference in overall survival between the ribociclib group and the placebo group, at a one-sided overall significance level of 2.5%, with the use of a log-rank test and three-look group sequential design. Because the difference between the groups in the primary end point of progression-free survival reached significance, the first interim analysis of overall survival was performed after 89 deaths (approximately 35% of the total 252 deaths) had occurred and did not cross the prespecified Lan–DeMets (O'Brien–Fleming) boundary (P value threshold of 0.00016). A protocol-specified second interim analysis of overall survival was to be performed after approximately 189 deaths had occurred (75% of the total 252 deaths). The prespecified Lan–DeMets (O'Brien–Fleming) stopping boundary criterion for this interim analysis was a P value threshold of 0.01018. Median overall survival was estimated with the use of the Kaplan–Meier method. The hazard ratio for death in the analysis of overall survival was estimated with the use of a stratified Cox proportional-hazards model. For the analysis of overall survival, data for patients were censored at the date the patient was last known to be alive.

RESULTS

PATIENTS AND TREATMENT

From December 17, 2014, to August 1, 2016, a total of 335 patients were randomly assigned to the ribociclib group, and 337 to the placebo group (Table S1 in the Supplementary Appendix, available at NEJM.org). Details regarding patient screening and the population included in the efficacy analysis have been published previously.[17] At the cutoff date for this analysis of overall survival, 173 patients were still receiving trial treatment: 116 of 335 patients (34.6%) in the ribociclib group and 57 of 337 (16.9%) in the placebo group. The median duration of follow-up was 34.6 months (minimum, 28.0 months). Patients and physicians remained unaware of the group assignments after the final analysis of progression-free survival. The median duration of exposure to trial treatment in the ribociclib group was approximately 2 years, which is 8 months longer than it was at the time of the primary analysis of progression-free survival. The median duration of exposure to placebo was approximately 1 year.

OVERALL SURVIVAL

This prespecified interim analysis of overall survival was performed after 192 deaths had occurred (83 among 335 patients [24.8%] in the ribociclib group and 109 among 337 [32.3%] in the placebo group). Kaplan–Meier estimated overall survival at 42 months was 70.2% (95% confidence interval [CI], 63.5 to 76.0) in the ribociclib group and 46.0% (95% CI, 32.0 to 58.9) in the placebo group (Table 1). Overall survival was significantly longer in the ribociclib group than in the placebo group, with a 29% lower risk of death (hazard ratio for death, 0.71; 95% CI, 0.54 to 0.95) (Fig. 1A). The one-sided stratified log-rank P value was 0.00973, which crossed the prespecified stopping boundary (P=0.01018) to claim superior efficacy of ribociclib. The median overall survival could not be estimated in the ribociclib group and was 40.9 months in the placebo group (95% CI, 37.8 to could not be estimated) (Fig. 1A). Because the efficacy stopping boundary was crossed, the results reported here showed the superiority of ribociclib to placebo with respect to the key secondary end point of overall survival, and, according to the protocol, are considered final.

Prespecified analyses of overall survival were performed in subgroups defined according to the endocrine therapy received. Among the 495 patients who received an aromatase inhibitor, 61 of 248 patients (24.6%) in the ribociclib group and 80 of 247 (32.4%) in the placebo group died. Estimated overall survival at 42 months among pa-

tients who received an aromatase inhibitor was 69.7% (95% CI, 61.3 to 76.7) in the ribociclib group and 43.0% (95% CI, 25.9 to 59.0) in the placebo group, and the hazard ratio for death was 0.70 (95% CI, 0.50 to 0.98) (Fig. 1B). Among the 177 patients who received tamoxifen, 22 of 87 patients (25.3%) in the ribociclib group and 29 of 90 (32.2%) in the placebo group died. Estimated overall survival at 42 months among patients who received tamoxifen was 71.2% (95% CI, 58.0 to 80.9) in the ribociclib group and 54.5% (95% CI, 36.0 to 69.7) in the placebo group, and the hazard ratio for death was 0.79 (95% CI, 0.45 to 1.38) (Fig. 1C).

Overall survival was also assessed in exploratory subgroups defined according to patient and disease characteristics, previous therapies, and geographic region (Fig. 2). In general, the overall survival benefit with ribociclib in these subgroups was consistent with that in the overall population; however, the small numbers of patients in some of these subgroups resulted in wide confidence intervals.

SUBSEQUENT THERAPY

A total of 219 patients in the ribociclib group and 280 patients in the placebo group discontinued the trial regimen. The percentage of these patients who received subsequent antineoplastic therapies was similar in the two groups: 151 patients (68.9%) in the ribociclib group and 205 (73.2%) in the placebo group (Table 2). Chemotherapy alone (22.4% in the ribociclib group and 28.6% in the placebo group) and hormone therapy alone (22.4% and 20.4%, respectively) were the most common first subsequent antineoplastic therapies. Pyrimidine analogues (29.7% in the ribociclib group and 33.6% in the placebo group) and taxanes (24.2% and 26.8%, respectively) were the most common chemotherapies in all subsequent lines of therapy. Aromatase inhibitors (29.2% in the ribociclib group and 27.5% in the placebo group) and antiestrogens (23.3% and 25.4%, respectively) were the most common hormone therapies. Post-treatment use of CDK4/6 inhibitors, including palbociclib, abemaciclib, and ribociclib, was lower in the ribociclib group than in the placebo group (10.0% vs. 18.6%) (Table S2 in the Supplementary Appendix).

In the intention-to-treat population, 234 patients received chemotherapy as a subsequent therapy at any time after the trial regimen was completed (95 in the ribociclib group and 139 in the placebo group). At 42 months, the estimated percentages of patients who had not yet received a first subsequent chemotherapy were 65.8% (95% CI, 59.1 to 71.7) in the ribociclib group and 49.0% (95% CI, 41.1 to 56.3) in the placebo group (hazard ratio for receipt of chemotherapy, 0.60; 95% CI, 0.46 to 0.77) (Fig. S1 in the Supplementary Appendix).

PROGRESSION-FREE SURVIVAL DURING RECEIPT OF SUBSEQUENT THERAPY

As of the data cutoff date, 287 patients (126 of 335 patients [37.6%] in the ribociclib group and 161 of 337 [47.8%] in the placebo group) had had disease progression while receiving subsequent therapy or had died from any cause. The estimated percentages of patients who were alive at 42 months and did not have disease progression while receiving second-line therapy were 54.6% (95% CI, 46.8 to 61.8) in the ribociclib group and 37.8% (95% CI, 28.4 to 47.2) in the placebo group (hazard ratio for disease progression or death, 0.69; 95% CI, 0.55 to 0.87) (Fig. 3).

ADVERSE EVENTS

Adverse events in the two groups remained consistent with those in the primary analysis (Table S3 in the Supplementary Appendix). Key grade 3 or 4 adverse events of special interest were neutropenia (in 63.5% of patients in the ribociclib group and 4.5% in the placebo group), hepatobiliary toxic effects (in 11% and 6.8%, respectively), and prolonged QT interval (in 1.8% and 1.2%, respectively).

DISCUSSION

In this trial, the addition of ribociclib to endocrine therapy resulted in significantly longer overall survival than endocrine therapy alone in patients with hormone-receptor–positive, HER2-negative advanced breast cancer. The overall survival benefit with ribociclib in the subgroup of patients who received aromatase inhibitors was similar to that in the overall intention-to-treat population, and the benefit was maintained across most patient subgroups. The overall survival results are consistent with those of progression-free survival, which were reported previously.[17] Because overall survival and postprogression outcomes are key factors in clinical decision making,

Subgroup	Patients	Ribociclib	Placebo	Hazard Ratio for Death (95% CI)
	no. (%)	*no. of deaths/total no. (%)*		
All patients	672 (100)	83/335 (24.8)	109/337 (32.3)	0.71 (0.54–0.95)
Endocrine therapy				
Tamoxifen and goserelin	177 (26.3)	22/87 (25.3)	29/90 (32.2)	0.79 (0.45–1.38)
NSAI and goserelin	495 (73.7)	61/248 (24.6)	80/247 (32.4)	0.70 (0.50–0.98)
ECOG score				
0	500 (74.4)	55/245 (22.4)	74/255 (29.0)	0.72 (0.50–1.02)
≥1	166 (24.7)	27/87 (31.0)	35/79 (44.3)	0.67 (0.40–1.12)
Age				
<40 yr	186 (27.7)	30/98 (30.6)	34/88 (38.6)	0.79 (0.48–1.30)
≥40 yr	486 (72.3)	53/237 (22.4)	75/249 (30.1)	0.68 (0.48–0.98)
Race				
Asian	198 (29.5)	16/99 (16.2)	37/99 (37.4)	0.40 (0.22–0.72)
Non-Asian	413 (61.5)	57/200 (28.5)	65/213 (30.5)	0.91 (0.64–1.30)
Previous chemotherapy in patients with metastatic disease				
Yes	94 (14.0)	13/47 (27.7)	19/47 (40.4)	0.67 (0.33–1.35)
No	578 (86.0)	70/288 (24.3)	90/290 (31.0)	0.73 (0.54–1.00)
Adjuvant or neoadjuvant chemotherapy				
Yes	276 (41.1)	46/138 (33.3)	51/138 (37.0)	0.91 (0.60–1.36)
No	302 (45.0)	24/150 (16.0)	39/152 (25.7)	0.54 (0.32–0.91)
Adjuvant or neoadjuvant hormonal therapy				
Yes	268 (39.9)	40/127 (31.5)	52/141 (36.9)	0.91 (0.60–1.39)
No	404 (60.1)	43/208 (20.7)	57/196 (29.1)	0.68 (0.45–1.00)
Hormone-receptor status				
Estrogen-receptor–positive and progesterone-receptor–positive	572 (85.1)	67/286 (23.4)	86/286 (30.1)	0.74 (0.54–1.02)
Other	100 (14.9)	16/49 (32.7)	23/51 (45.1)	0.64 (0.33–1.22)
Geographic region				
Asia	180 (26.8)	16/92 (17.4)	34/88 (38.6)	0.43 (0.24–0.78)
Europe and Australia	275 (40.9)	39/136 (28.7)	42/139 (30.2)	0.97 (0.62–1.52)
Latin America	56 (8.3)	9/31 (29.0)	9/25 (36.0)	0.63 (0.23–1.70)
North America	97 (14.4)	12/47 (25.5)	16/50 (32.0)	0.86 (0.40–1.87)
Other	64 (9.5)	7/29 (24.1)	8/35 (22.9)	0.78 (0.27–2.25)
Lung or liver involvement				
Yes	342 (50.9)	50/173 (28.9)	62/169 (36.7)	0.73 (0.50–1.05)
No	330 (49.1)	33/162 (20.4)	47/168 (28.0)	0.70 (0.48–1.09)
Bone lesion only				
Yes	159 (23.7)	19/81 (23.5)	18/78 (23.1)	1.00 (0.53–1.93)
No	513 (76.3)	64/254 (25.2)	91/259 (35.1)	0.65 (0.47–0.90)
No. of sites of metastasis				
<3	436 (64.9)	50/219 (22.8)	60/217 (27.6)	0.85 (0.58–1.25)
≥3	236 (35.1)	33/116 (28.4)	49/120 (40.8)	0.58 (0.37–0.91)
Time from previous endocrine therapy completion				
None	404 (60.1)	43/208 (20.7)	57/196 (29.1)	0.68 (0.45–1.00)
Progression ≤12 mo after end of endocrine therapy	205 (30.5)	35/100 (35.0)	46/105 (43.8)	0.80 (0.51–1.27)
Progression >12 mo after end of endocrine therapy	60 (8.9)	5/25 (20.0)	6/35 (17.1)	1.53 (0.44–5.34)

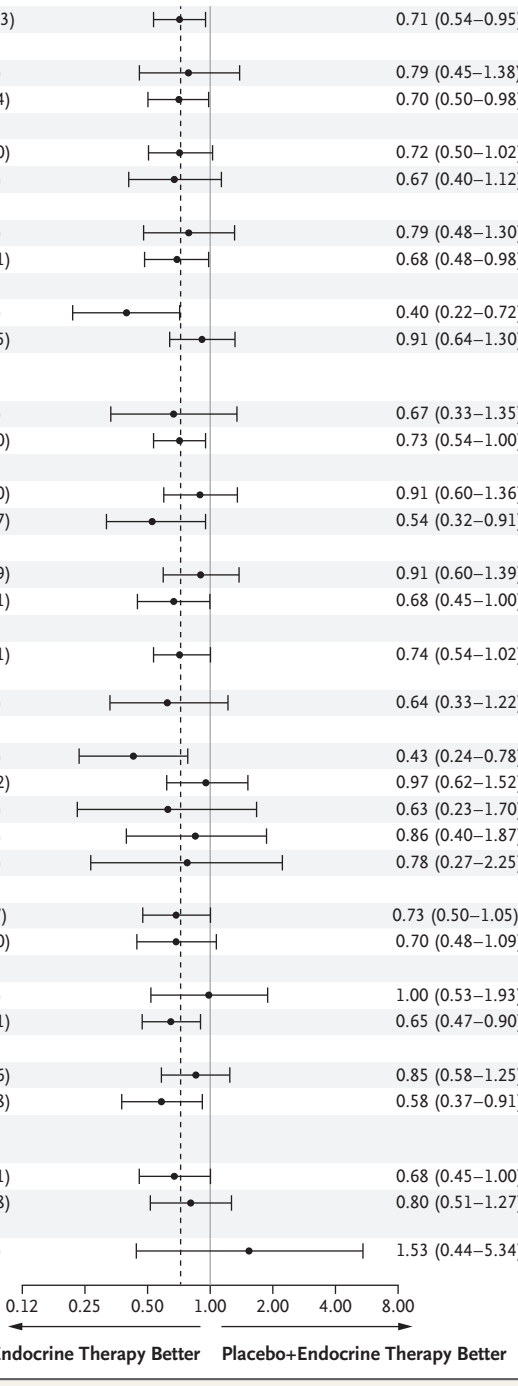


Figure 2. Exploratory Analyses of Overall Survival in Subgroups.

Percentages may not total 100 because of rounding. Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability. Race was reported by the patient. The adjuvant or neoadjuvant chemotherapy subgroup includes only patients who had not received chemotherapy after a diagnosis of metastatic disease (before enrollment in the trial). The dashed vertical line indicates the hazard ratio of 0.71 for the overall population.

Table 2. First Subsequent Antineoplastic Therapy among Patients Who Discontinued the Trial Regimen.

Variable	Ribociclib Group (N=335)	Placebo Group (N=337)
No. of patients who discontinued the trial regimen	219	280
Patients who received any subsequent therapy — no. (%)	151 (68.9)	205 (73.2)
Chemotherapy alone	49 (22.4)	80 (28.6)
Chemotherapy plus hormone therapy or other therapy*	18 (8.2)	22 (7.9)
Hormone therapy alone	49 (22.4)	57 (20.4)
Hormone therapy plus other therapy†	31 (14.2)	41 (14.6)
Other	4 (1.8)	5 (1.8)

* This category includes patients who received chemotherapy in combination with any nonchemotherapy.
† This category includes patients who received hormone therapy plus another medication without chemotherapy.

the results of adding biologic treatments to endocrine therapies in early lines of therapy are highly relevant in this patient population. Additional analysis of progression-free survival while patients were receiving subsequent therapy indicates that the benefit of ribociclib was seen over the combined period of first-line and second-line therapies.

After a median of 2 years of treatment exposure in the ribociclib group, no new safety signals were observed.[17] As reported previously, in the ribociclib group, more instances of QT-interval prolongation were observed in patients who received tamoxifen than in those who received an aromatase inhibitor. QT-interval prolongation was also observed in patients in the placebo group who received tamoxifen.[17] No instances of symptomatic arrhythmias or torsades de pointes have been observed in this trial.

Recently, the PALOMA-3 trial assessed overall survival with either palbociclib or placebo plus fulvestrant in patients with hormone-receptor–positive, HER2-negative advanced breast cancer; overall survival was not significantly longer in the palbociclib group than in the placebo group in the overall population or in the subgroup of premenopausal patients.[23] There are key differences between the PALOMA-3 and MONALEESA-7 trials beyond the endocrine therapy that was used. The PALOMA-3 trial included premenopausal and postmenopausal patients who were more heavily pretreated, whereas all patients in the MONALEESA-7 trial were premenopausal or perimenopausal and were receiving initial endocrine therapy. These differences may limit the applicability of cross-trial comparisons. Furthermore, chemotherapy pretreatment in the setting of advanced disease — a possible indication of a higher-risk population — was less common in the MONALEESA-7 trial than in the PALOMA-3 trial (14% and 34%, respectively).[17,21]

The improvement in overall survival with ribociclib that was observed in this planned interim analysis in the MONALEESA-7 trial was significant, even though 18.6% of patients who discontinued the trial regimen in the placebo group received CDK4/6 inhibitors as subsequent therapy. One possible explanation for this treatment effect of ribociclib could be the premenopausal patient population. Few data are available from large phase 3 trials of targeted therapy for this population, and breast cancer is more aggressive in these patients, since it is more likely that the luminal B subtype is present and that there is lower expression of estrogen receptor 1.[1,2,29] In addition, differences exist among the CDK4/6 inhibitors in terms of pharmacokinetics (e.g., half-life and time to maximum concentration) and selectivity for CDK4 as compared with CDK6 (e.g., ribociclib is four times more selective for CDK4 than for CDK6).[30,31] In addition, ribociclib may have a different level of selectivity for other cyclin-dependent kinase complexes than the other CDK4/6 inhibitors, and it has been hypothesized that such differences could potentially be clinically relevant.[30-32]

The significantly longer progression-free survival in the ribociclib group than in the placebo group in the previous report of the MONALEESA-7 trial[17] and the approximately 29% lower risk of death in the ribociclib group in this report show

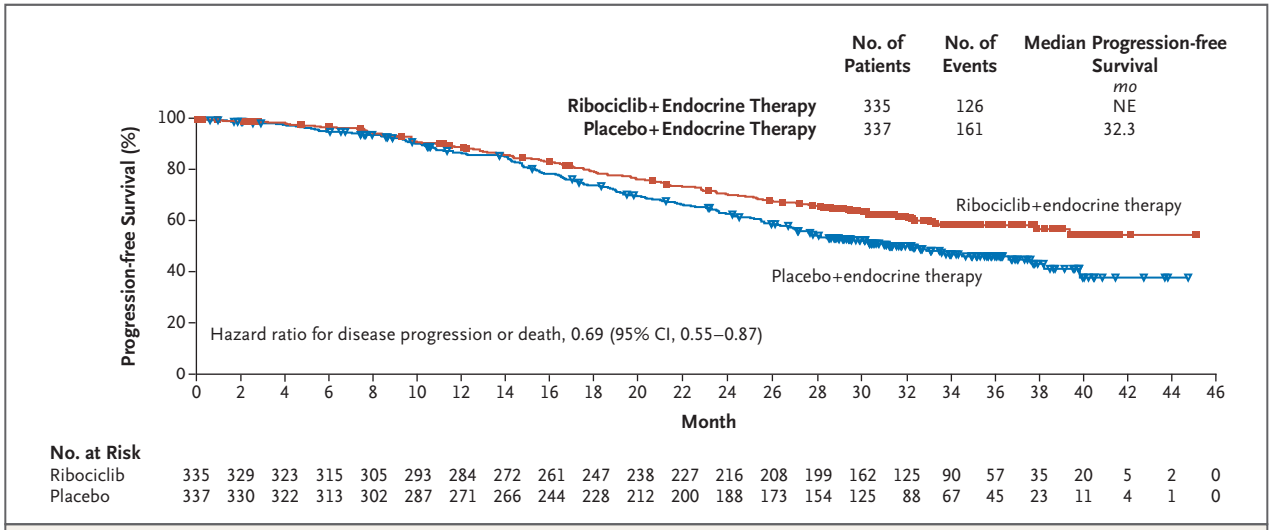


Figure 3. Progression-free Survival during Receipt of Subsequent Therapy or Death from Any Cause.

Progression-free survival during receipt of subsequent therapy was defined as the time from randomization to the first documented disease progression while the patient was receiving second-line therapy (as reported by the physician) or to death from any cause, whichever occurred first. The squares and triangles indicate censored data.

that there is a substantial clinical benefit of ribociclib plus endocrine therapy as compared with endocrine therapy alone. No new concerns regarding toxic effects were noted with longer follow-up.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. N Engl J Med. DOI: 10.1056/NEJMoa1903765

SUPPLEMENTARY APPENDIX

Supplement to: Im S-A, Lu Y-S, Bardia A, et al. Overall Survival with Ribociclib Plus Endocrine Therapy in Breast Cancer.

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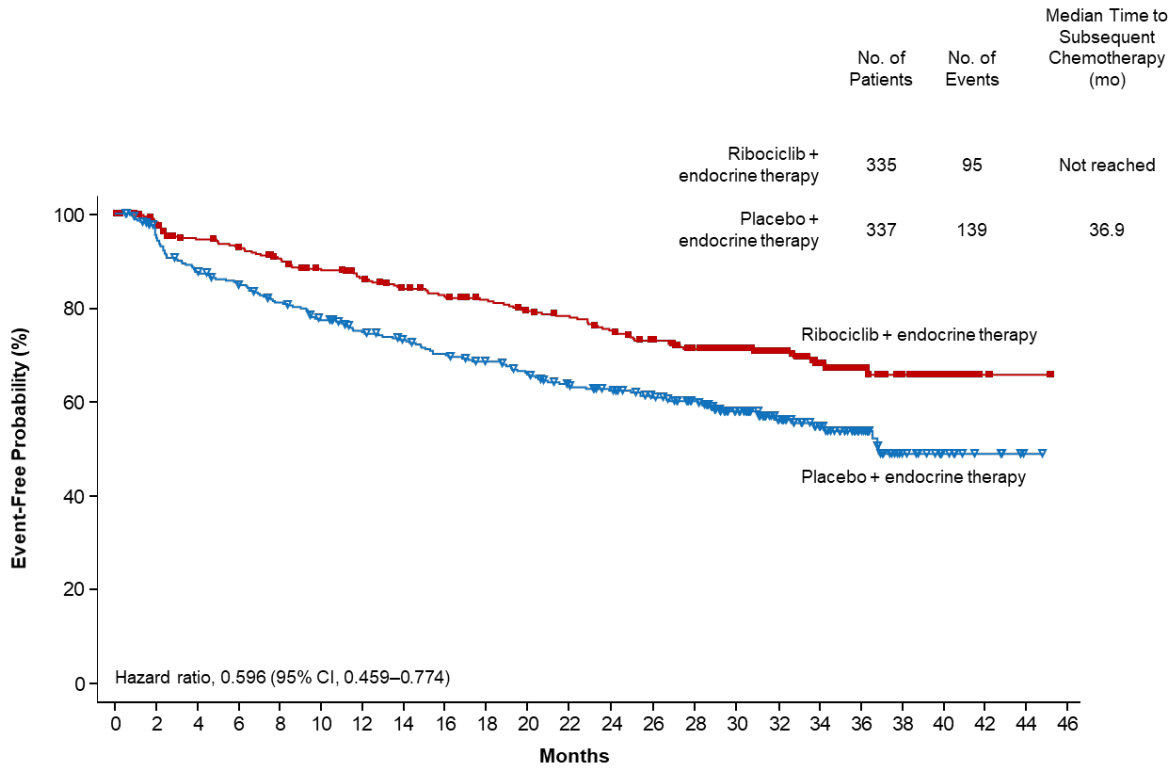
Table S1. Patient Disposition.

	Ribociclib + Endocrine Therapy (n=335)	Placebo + Endocrine Therapy (n=337)	All Patients (N=672)
Patients treated — no. (%)	335 (100)	337 (100)	672 (100)
Treatment ongoing*	116 (34.6)	57 (16.9)	173 (25.7)
Ended treatment	219 (65.4)	280 (83.1)	499 (74.3)
Reason for end of treatment — no. (%)			
Adverse event	11 (3.3)	13 (3.9)	24 (3.6)
Loss to follow-up	2 (0.6)	0	2 (0.3)
Physician decision	10 (3.0)	22 (6.5)	32 (4.8)
Progressive disease	173 (51.6)	230 (68.2)	403 (60.0)
Protocol deviation	0	2 (0.6)	2 (0.3)
Patient/guardian decision	20 (6.0)	10 (3.0)	30 (4.5)
Death	3 (0.9)	3 (0.9)	6 (0.9)
Entered survival follow-up†	192 (87.7)	259 (92.5)	451 (90.4)

* Patients continuing study treatment at the time of data cutoff (November 30, 2018).

† The percentage of patients who entered survival follow-up uses the number of patients with end of treatment as the denominator.

Figure S1. Time to First Subsequent Chemotherapy. Tick marks indicate censored data.



No. of Patients Still at Risk

Ribociclib	335	324	307	299	288	275	267	255	247	240	231	225	216	206	195	158	125	90	54	35	21	5	2	0
Placebo	337	315	288	277	261	246	232	223	212	204	194	181	174	161	147	119	86	67	42	20	11	6	1	0

Table S2. Summary of All Lines of Subsequent Antineoplastic Medications by Drug Type.

	Ribociclib + Endocrine Therapy (n=335)	Placebo + Endocrine Therapy (n=337)
Patients who discontinued study treatment, n	219	280
Any medication — no. (%)	151 (68.9)	205 (73.2)
Chemotherapy		
Pyrimidine analogues	65 (29.7)	94 (33.6)
Taxanes	53 (24.2)	75 (26.8)
Platinum compounds	25 (11.4)	31 (11.1)
Anthracyclines*	24 (11.0)	36 (12.9)
Hormone therapy — no. (%)		
Aromatase inhibitors	64 (29.2)	77 (27.5)
Exemestane	36 (16.4)	36 (12.9)
Letrozole	28 (12.8)	39 (13.9)
Anastrozole	7 (3.2)	7 (2.5)
Anti-estrogens	51 (23.3)	71 (25.4)
Fulvestrant	41 (18.7)	56 (20.0)
Tamoxifen	13 (5.9)	17 (6.1)
Luteinizing hormone-releasing hormone agonists	37 (16.9)	48 (17.1)
Kinase inhibitors — no. (%)		
Everolimus	26 (11.9)	30 (10.7)
Palbociclib†	21 (9.6)	42 (15.0)
Abemaciclib†	1 (0.5)	1 (0.4)
Ribociclib†	0	9 (3.2)
Other	3 (1.4)	1 (0.4)

* Includes substances related to anthracycline.

† In total, 22 patients in the ribociclib arm and 52 patients in the placebo arm received subsequent CDK4/6 inhibitor treatment.

Table S3. Adverse Events of Special Interest, Irrespective of Causality.

Adverse event special interest Grouping	Ribociclib + Endocrine Therapy (n=335)			Placebo + Endocrine Therapy (n=337)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic AESI — no. (%)						
Neutropenia	259 (77.3)	174 (51.9)	39 (11.6)	29 (8.6)	12 (3.6)	3 (0.9)
Leukopenia	117 (34.9)	50 (14.9)	4 (1.2)	20 (5.9)	5 (1.5)	1 (0.3)
Anemia	75 (22.4)	12 (3.6)	0	37 (11.0)	8 (2.4)	0
Thrombocytopenia	31 (9.3)	2 (0.6)	1 (0.3)	8 (2.4)	1 (0.3)	1 (0.3)
Other	1 (0.3)	0	1 (0.3)	0	0	0
Nonhematologic AESI — no. (%)						
Infections	180 (53.7)	16 (4.8)	0	140 (41.5)	8 (2.4)	0
Hepatobiliary toxicity	92 (27.5)	35 (10.4)	2 (0.6)	77 (22.8)	21 (6.2)	2 (0.6)
Pulmonary toxicity*	85 (25.4)	4 (1.2)	1 (0.3)	65 (19.3)	1 (0.3)	1 (0.3)
QT interval prolongation	42 (12.5)	6 (1.8)	0	21 (6.2)	3 (0.9)	1 (0.3)
Renal toxicity	12 (3.6)	1 (0.3)	0	5 (1.5)	1 (0.3)	1 (0.3)
Pulmonary embolism	9 (2.7)	4 (1.2)	1 (0.3)	3 (0.9)	2 (0.6)	0
Pulmonary toxicity†	1 (0.3)	0	0	0	0	0
Reproductive toxicity	0	0	0	0	0	0

* Includes respiratory disorders, such as cough, dyspnea, etc.

† Includes interstitial lung disease.